Controversy

Can fetuses feel pain?

Stuart W G Derbyshire

Legal or clinical mandates to prevent pain in fetuses are based on limited evidence and may put women seeking abortion at unnecessary risk. This paper outlines neurodevelopment in fetuses in the context of pain experience

The US federal government is considering legislation that will require doctors to inform women seeking abortions that "there is substantial evidence that the process of being killed in an abortion will cause the unborn child pain."[w1] The bill mandates that a fetus of more than 22 weeks' gestational age should receive pain reducing drugs before an abortion. Doctors who fail to comply can be fined $100 000 (£57 700; €84 000) and can lose their licence and Medicaid funding.

In the United Kingdom provocative images of the fetus generated by four dimensional ultrasonography have fuelled a reassessment of fetal capabilities along with suggestions that the fetus can respond both emotionally and cognitively. Subsequent political and media discussion in the United Kingdom has debated changing abortion laws and procedures to mitigate against fetal pain.[w2 w3]

This paper discusses whether there is sufficient evidence to support a concept of fetal pain through an examination of fetal neurobiology and the relation to experience. Important neurobiological developments occur at 7, 18, and 26 weeks' gestation and are the proposed periods for when a fetus can feel pain. Although the developmental changes during these periods are remarkable they do not tell us whether the fetus can experience pain. The subjective experience of pain cannot be inferred from anatomical developments because these developments do not account for subjectivity and the conscious contents of pain.

The neurobiology of the fetus: anatomical pathways

Notwithstanding limitations, it is useful to view the pain system as an alarm system. Viewed in this way, a noxious stimulus is an event that activates free nerve endings in the skin, similar to pushing an alarm button. The electric cable from the button to the alarm is similar to the connection between the nerve endings and the brain. The brain is the alarm that rings out pain. Whether the fetus can respond to a noxious stimulus with pain can thus be decided in part by determining when the alarm system is completely developed.

Free nerve endings, the "alarm buttons," begin to develop at about seven weeks' gestation[1 2]; projections from the spinal cord, the major "cable" to the brain, can reach the thalamus (the lower alarm) at seven weeks' gestation.[3] An intact spinothalamic projection might be viewed as the minimal necessary anatomical architecture to support pain processing, putting the lower limit for the experience of pain at seven weeks' gestation.

At this time, however, the nervous system has yet to fully mature. No laminar structure is evident in the thalamus or cortex, a defining feature of maturity.[4 5]

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Can a fetus experience pain?

The external wall of the brain is about 1 mm thick and consists of an inner and outer layer with no cortical plate. The neuronal cell density of the outer layer is much higher than that of a newborn infant or adult and at seven weeks' gestation has yet to receive any thalamic projections. Without thalamic projections, these neuronal cells cannot process noxious information from the periphery.

The first projections from the thalamus to cortex (the higher alarm) appear at 12-16 weeks' gestation. By this stage the brain's outer layer has split into an outer cortical rim, with a subplate developing below. The thalamic projections that develop from 12-16 weeks penetrate the subplate. Within the subplate, cortical afferents establish prolonged synaptic contacts before entering the cortical plate. The subplate is a "waiting compartment," required for mature connections in the cortex.[6 7] The major afferent fibres (thalamocortical, basal forebrain, and corticocortical) can wait in the subplate for several weeks, before they penetrate and form synapses within the cortical plate from 23-25 weeks' gestation. Subsequent dissolution of the subplate occurs through prolonged growth and maturation of associative connections in the human cerebral cortex.

Spinothalamic projections into the subplate may provide the minimal necessary anatomy for pain experience,[8] but this view does not account for the transient nature of the subplate and its apparent role in the maturation of functional cortical connections.[6] A

References w1-w18 are on bmj.com

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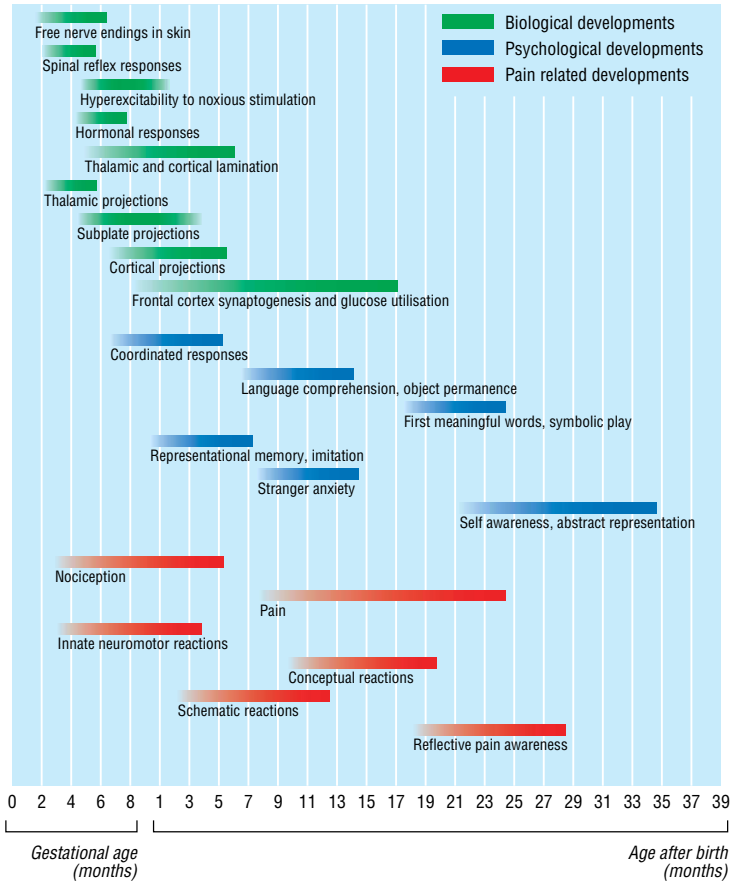

Key developmental stages before and after birth. Colours illustrate gradual emergence of indicated feature. Solid colour indicates that feature is clearly apparent although not necessarily fully developed (frontal cortex synaptogenesis, for example, continues into adolescence). Colour becoming dim again indicates that feature is transient (hyperexcitability to noxious stimulation, for example, appears at about four months' gestation but is no longer a feature of behaviour after three months of age). See text and earlier reviews[w4-w6] for further details

lack of functional neuronal activity within the subplate calls into question the pain experience of a fetus before the penetration of spinothalamic fibres into the cortical plate.

Current theories of pain consider an intact cortical system to be both necessary and sufficient for pain experience.[9 10] In support are functional imaging studies showing that activation within a network of cortical regions correlate with reported pain experience.[9] Furthermore, cortical activation can generate the experience of pain even in the absence of actual noxious stimulation.[10] These observations suggest thalamic projections into the cortical plate are the minimal necessary anatomy for pain experience. These projections are complete at 23 weeks' gestation. The period 23-25 weeks' gestation is also the time at which the peripheral free nerve endings and their projection sites within the spinal cord reach full maturity.[1] By 26 weeks' gestation the characteristic layers of the thalamus and cortex are visible, with obvious similarities to the adult brain,[6 7] and it has recently been shown that noxious stimulation can evoke haemodynamic changes in the somatosensory cortex of premature babies from a gestational age of 25 weeks.[11] Although the system is clearly immature and much development is still to occur (fig 1), good evidence exists that the biological system necessary for pain is intact and functional from around 26 weeks' gestation.

Investigating fetal psychology

Without verbal reports and direct access to the mind of a fetus, inferences about what fetuses are able to experience depend on the interpretation of secondary evidence. As discussed, neuroanatomical pathways necessary for processing pain, similar to those observed in adults and older children, could be in place by 23 weeks' gestation. The stereotypical hormonal stress response of adults or older infants, of about 18 months onwards, reporting pain is observable in fetuses at 18 weeks' gestation.[12] Behavioural reactions and brain haemodynamic responses to noxious stimuli, comparable to adults or older infants, occur by 26 weeks' gestation.[11 13] These and other observations (figure) are taken to suggest that the fetal mind can support an experience of pain from at least 26 weeks' gestation.[8 14]

Inferences of fetal pain from such indirect evidence, however, present considerable difficulties. One is that many environmental factors inherent to the womb provide for a distinction between the environment of fetuses and that of neonates.[15] The placenta provides a chemical environment to encourage sleep and to suppress higher cortical activation in the presence of intrusive external stimulation. The environment of the womb consists of warmth, buoyancy, and a cushion of fluid to prevent tactile stimulation. In contrast to this buffered environment, the intense tactile stimulation of birth and the subsequent separation of the neonate from the placenta, facilitate the rapid onset of behavioural activity and wakefulness in the newborn infant. Birth marks the transition from laying down brain tissue while in the womb to organising that tissue for the wider world outside the womb.

Another obstacle to equating fetal pain experience with that of adults or older children is the developmental process that begins after birth. Theories of development assume that the early human mind begins with minimal content and gradually evolves into the rich experience of older children and adults.[16 17] Although the view of a neonate as a blank slate, or tabula rasa, is generally rejected, it is broadly accepted that psychological processes have content concerning people, objects, and symbols, which lay in the first instance outside the brain.[16 17 w7-w9] If pain also depends on content derived from outside the brain, then fetal pain cannot be possible, regardless of neural development.

The content of pain

Few living creatures are unresponsive to a noxious stimulus (for example, a pinch or burning flame). Light a flame next to a fruit fly larva, for example, and it will bend and roll away.[w10] These responses depend on specialised sensory neurones, similar to free nerve endings in humans, which preferentially respond to stimuli that can damage tissue. Although the larva clearly has a biological apparatus to detect and respond to dangerous stimuli, can it be said to feel pain?

If the larva feels pain, then it presumably has some conscious or mental representation of the pain. The pain must consist of such experienced concepts as the location, feel, and cognition associated with the pain.

Without this content, there is the response to noxious events, otherwise known as nociception, but no pain. The larva thus cannot be said to have the capacity for pain: there is no evidence for the conceptual content that the experience of pain implies.

A proper understanding of pain must account for the conceptual content that constitutes the pain experience. The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[w11] By this definition pain is not merely the response to noxious stimuli or disease but is a conscious experience. The definition further states that "pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life."[w11] The limited neural system of fetuses cannot support such cognitive, affective, and evaluative experiences; and the limited opportunity for this content to have been introduced also means that it is not possible for a fetus to experience pain.

The developmental process

Without consciousness there can be nociception but there cannot be pain. Thus to understand how pain experience becomes possible it is necessary to understand the origin and developmental course of conscious experience. It is reasonable to assume that conscious function can only emerge if the necessary neural circuitry to carry out that function is fully developed and functional.[18 19 w5]

It is also necessary to assume that conscious function can only emerge if the proper psychological content and environment has been provided.[16 17] Before infants can think about objects or events, or experience sensations and emotion, the contents of thought must have an independent existence in their mind. This is something that is achieved through continued brain development in conjunction with discoveries made in action and in patterns of mutual adjustment and interactions with a caregiver. The development of representational memory, which allows infants to respond and to learn from stored information rather than respond to material directly available, may be considered a building block of conscious development. Representational memory begins to emerge as the frontal cortex develops between two and four months of age, supported by developments in the hippocampus that facilitate the formation, storage, and retrieval of memories.[w5] From this point tagging in memory is possible, or labelling as "something," all the objects, emotions, and sensations that appear or are felt. When a primary caregiver points to a spot on the body and asks "does that hurt?" he or she is providing content and enabling an internal discrimination and with it experience. This type of interaction provides content and symbols that allow infants to locate and anchor emotions and sensations. It is in this way that infants can arrive at a particular state of being within their own mind. Although pain experience is individual, it is created by a process that extends beyond the individual.[16 17 w9]

This is likely to strike anyone as strange because it is simply not how we intuitively believe pain to be. Because pain is so automatic and personal we perceive it to be natural and private. But because we are able to experience pain as such a personal event does not mean that we individually acquired the ability to experience pain in the first place. Nor does it mean that the psychological mechanisms by which we experience pain arose within our own brains by some individualistic process such as neuronal maturation.[16 w9]

This is not to deny that neonates and fetuses have the neural apparatus to discriminate information; clearly, fetuses and neonates do not respond to tactile stimuli in the same way as they do to auditory stimuli, for example. Indeed, this discriminatory processing is the raw material for a primary caregiver's assessments of his or her infant's need and for the interactions and behavioural adjustments that occur in the forthcoming months. Innate neural and behavioural discrimination are part of the material for developing experiential discrimination, but experiential discrimination is yet to develop and relies critically on interactions with a primary caregiver. For fetuses and newborn infants, these interactions have yet to occur.

By this line of reasoning fetuses cannot be held to experience pain. Not only has the biological development not yet occurred to support pain experience, but the environment after birth, so necessary to the development of pain experience, is also yet to occur.

Clinical and policy implications

Earlier beliefs by anaesthetists that newborns and neonates could not feel pain led to an under-utilisation of analgesics.[14 w12-w14] Before controlled trials,[w15 w16] however, there were justified concerns about intraoperative hypotension caused by the anaesthesia of infants, and about postanaesthesia apnoea and respiratory depression by narcotic analgesia. Sufficient evidence now shows that such risks during procedures on neonates and infants are outweighed by the clinical benefits, regardless of whether evidence supports or negates the concept of pain in neonates. Should anaesthetists return to a view that neonates cannot feel pain, the clinical benefits of anaesthetic intervention will remain. A lack of pain experience provides no ethical or practical reason to justify returning to a regimen of fewer anaesthetics or analgesic intervention.

As more centres begin to carry out open and closed fetal surgery,[w17] enthusiasm for analgesia and anaesthesia in fetuses is likely to increase. It is tempting to assume that what benefits neonates will also benefit fetuses. However the greater immaturity of fetuses and their different hormonal and physical environment indicate that clinical trials should be carried out with fetal patients to show improved outcomes. Currently no defined evidence based fetal anaesthesia or analgesia protocol exits for these procedures.

The medical goals of survival and long term normal development of fetuses should not influence medical decisions when a woman seeks an abortion.[20] Under these circumstances, the question of analgesia or anaesthesia in fetuses can be more directly tackled by examining the possibility of pain in fetuses and the consequences of any pain relief for fetuses on the health and wellbeing of the pregnant woman. The case against fetal pain, as documented here, indicates that a mandate to provide pain relief before abortion is not supported by what is known about the neurodevelopment of systems that support pain. Proposals to directly inject fetuses with fentanyl[w18] or to provide pain relief through

Summary points

The neuroanatomical system for pain can be considered complete by 26 weeks' gestation

A developed neuroanatomical system is necessary but not sufficient for pain experience

Pain experience requires development of the brain but also requires development of the mind to accommodate the subjectivity of pain

Development of the mind occurs outside the womb through the actions of the infant and mutual adjustment with primary caregivers

The absence of pain in the fetus does not resolve the morality of abortion but does argue against legal and clinical efforts to prevent such pain during an abortion

increased administration of fentanyl or diazepams to pregnant women, which increase risks to the women and costs to the health provider, undermine the interests of the women and are unnecessary for fetuses, who have not yet reached a developmental stage that would support the conscious experience of pain.

Conclusion

The neural circuitry for pain in fetuses is immature. More importantly, the developmental processes necessary for the mindful experience of pain are not yet developed. An absence of pain in the fetus does not resolve the question of whether abortion is morally acceptable or should be legal. Nevertheless, proposals to inform women seeking abortions of the potential for pain in fetuses are not supported by evidence. Legal or clinical mandates for interventions to prevent such pain are scientifically unsound and may expose women to inappropriate interventions, risks, and distress. Avoiding a discussion of fetal pain with women requesting abortions is not misguided paternalism[21] but a sound policy based on good evidence that fetuses cannot experience pain.

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Corrections and clarifications

Treating refractory epilepsy in adults

We made some last minute page changes to this editorial by Edward Reynolds to keep the editorials section within the required number of pages that week (*BMJ* 2006;332:562-3, 11 Mar). Unfortunately, this led to some weakening of the author's arguments. The following sentence should be reinstated after the first sentence of the article: "Before the 1970s such patients were invariably treated with polytherapy, often with combined capsules of phenobarbital and phenytoin." A further sentence should be reinstated after the second sentence of the final paragraph: "The priority of industry is the marketing of new drugs by short term, placebo controlled trials that show efficacy without unacceptable toxicity to the satisfaction of regulatory and licensing authorities." And the final sentence of the article should have continued, "especially as the NICE guidelines suggest that claims that the newer drugs are associated with a better quality of life rest on weak or inadequate evidence.[8]"

Unrelated to the above editorial cuts, we also failed to publish the following competing interests statement that the author had already supplied to us: "I undertook clinical studies of monotherapy and polytherapy in newly diagnosed and refractory patients in the 1970s and 1980s for which I received funding from the Medical Research Council and several pharmaceutical companies."

Effect of combinations of drugs on all cause mortality in patients with ischaemic heart disease: nested case-control analysis

The authors of this article by Julia Hippisley-Cox and Carol Coupland, published last year, have advised us that a reference was wrong (*BMJ* 2005;330:1059-63, 7 May). Reference 16 should be:

PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004;351:2058-68.